Remarks

Formal Matters

Applicants note with appreciation that the Office has withdrawn the claim objections and the 35 U.S.C. § 112, first and second paragraph rejections.

Information Disclosure Statement

Applicants thank the Examiner for acknowledging receipt of the Information Disclosure Statements filed on September 25, 2008 and for returning electronically signed copies of the Forms PTO-1449 submitted therein.

Claim Rejections under 35 U.S.C. § 102(b)/103

Claims 1-3

The Action rejects claims 1 and 2 under 35 U.S.C. § 102(b) as allegedly being anticipated by Drysdale et al., (Developmental Biology (1997), vol. 188, p. 205-215). The Action states that Drysdale et al. disclose a method for forming autonomically beating cardiac muscle-like cell aggregates from stem cells derived from a vertebrate *in vitro*. The Action also rejects claims 1-3 under 35 U.S.C. § 103(a) as allegedly being obvious over Drysdale et al. in view of Takahashi et al. (Journal of Medicinal Chemistry, August 2002, Vol. 45, No. 16, p. 3327-3330), relying on Drysdale et al. to disclose a method for forming autonomically beating cardiac muscle-like cell aggregates from stem cells derived from a vertebrate *in vitro* and Takahashi et al. to disclose at least one compound, namely PA024, a retinoic acid X receptor ligand recited in claim 3.

Applicants respectfully traverse the rejections. Applicants submit that Drysdale et al. do not anticipate claims 1 and 2, and Drysdale et al. in view of Takahashi et al. do not render obvious claims 1-3.

Applicants initially note that, contrary to the Office's position, Drysdale et al. do not teach "[a] method for forming autonomically beating cardiac muscle-like cell aggregates from stem cells derived from a vertebrate animal in vitro, which comprises culturing the stem cells derived from a vertebrate animal in the presence of a retinoic acid X receptor ligand." Rather, Drysdale et al. teach "that exogenous [retinoic acid] can completely block the differentiation of the myocardium when applied at a relatively late stage in the cardiogenic program" (page 211, column 1, last paragraph). In other words, Drysdale et al. teach that an embryo that is *not* treated with RA will give rise to cardiac tissue, while treatment of an embryo RA will induce dysfunction of cardiac tissue due to possible suppression of a differentiating factor by RA.

Applicants further note that since Drysdale et al. teach that *RA prevents* myocardial differentiation, Drysdale et al. thereby *cannot teach a method for forming autonomically beating cardiac muscle-like cell aggregates*. In fact, Drysdale et al. specifically states that the dysfunctional heart tube created after treating the tissue with RA, "*never forms beating tissue*" (emphasis added) (abstract). Applicants note that it would not be a logical conclusion to find that Drysdale et al. teach the present invention, when Drysdale et al. teach that RA creates a non-beating heart, while the present invention claims a method of forming an autonomically beating cardiac muscle-like cell aggregates. Applicants submit that Drysdale et al. do not anticipate claims 1 and 2 of the present invention.

Applicants also submit that the organism used in Drysdale et al. is *not* a pluripotent stem cell capable of generating a number of different cell types, but rather an *embryo* in which the

tissues and cells were already destined to differentiate. Drysdale et al. do not culture stem cells while the cells are pluripotent, and moreover, do not culture cells in the presence of a retinoic acid X receptor ligand at the stage where the cells would be pluripotent. Rather, Drysdale et al. use an *embryo* that is already destined to differentiate in its normal course, into tissue or organs. Applicants submit that Drysdale et al. fail to anticipate the claimed invention.

Applicants further submit that claims 1-3 are not obvious under Drysdale et al. in view of Takahashi et al. because, alone or in combination, Drysdale et al. and Takahashi et al. do not teach all the elements of the claimed invention. Applicants note that Drysdale et al., as described above, do not teach all the elements of the claimed invention. Takahashi et al. is merely cited for its disclosure of a retinoic acid X receptor ligand and fails to remedy the deficiencies of Drysdale et al. Thus, Applicants submit that even if Drysdale et al. were combined with Takahashi et al., the present invention would not result.

Applicants also respectfully submit that there is no reason to modify or combine the teachings of Drysdale et al. in view of Takahashi et al. to arrive at the presently claimed invention. While the *KSR* court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007) (quoting *KSR International Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1731 (2007)).

Applicants submit that the motivation asserted by the Office for combining the cited documents would not have prompted a person of ordinary skill in the relevant field to arrive at

the present invention as it is claimed. The Action states that the motivation to combine Drysdale et al. and Takahashi et al. was "the role of retinoic acid receptor in heart development" as discussed in Drysdale et al. (Office Action, page 7). However, Applicants respectfully submit that if a person of skill in the art were to consider Drysdale et al.'s teaching with respect to the role of the retinoic acid receptor in heart development, which clearly shows that RA-treated tissue does *not* differentiate into heart tissue, that person would *not* have been led to expose stem cells to RA with any expectation of producing cardiac tissue. Indeed, if anything, Drysdale et al. leads one skilled in the art in a direction completely opposite the claimed invention. And Takahashi et al. does nothing to change that direction – there is nothing in Takahashi et al. that would lead one skilled in the art to create autonomically beating cardiac muscle-like cell aggregates from stem cells derived from a vertebrate animal in vitro, by culturing the stem cells derived from a vertebrate animal in the presence of a retinoic acid X receptor ligand.

In view of the foregoing, Applicants respectfully request withdrawal of the outstanding rejections under 35 U.S.C. § 102(b) and 35 U.S.C. § 103.

Claims 7 and 8

The Action also rejects claim 7 under 35 U.S.C. § 102(b) as allegedly anticipated by Moriya et al. (Develop. Growth Differ. (2000), vol. 42, pp. 593-602). The Action asserts that Moriya allegedly discloses the formation of pancreas tissue from undifferentiated cells from *Xenopus* in the presence of all-*trans*-retinoic acid. The Action also rejects claims 7 and 8 under 35 U.S.C. § 103(a) as allegedly being obvious over Moriya et al. in view of Takahashi et al. (J. Med. Chem. (2002), vol. 45, no. 16, pp. 3327-330). The Action alleges that Moriya discloses the formation of pancreas tissue from undifferentiated cells from *Xenopus* in the presence of all-

trans-retinoic acid and Takahashi et al. allegedly discloses the RAR ligand 4-[(5, 6, 7, 8, -tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl) carbamoyl] as recited in claim 8.

Applicants respectfully traverse the rejections. Applicants submit that Moriya et al. do not anticipate claim 7 of the claimed invention, and Moriya et al. in view of Takahashi et al. do not render obvious claims 7 and 8.

Applicants submit that Moriya et al. do not teach "[a] method for forming a tissue having morphology and function of a pancreas from stem cells derived from a vertebrate animal in vitro, which comprises culturing the stem cells derived from a vertebrate animal in the presence of a retinoic acid receptor ligand, together with activin, wherein said retinoic acid receptor ligand does not substantially bind to the retinoic acid receptor subtype γ."

Applicants note that Moriya et al. teach that when a part of an embryonic ectoderm, which is already in a differentiation state and destined to give rise to specific epidermis and neural tissues, is treated with RA, the direction of the differentiation is influenced to differentiate into different tissues from those originally programmed by normal differentiation. For example, Moriya et al. states that "retinoic acid may only be able to induce pancreas that *have already differentiated* into endomesoderm," (emphasis added) (page 598, right column, last sentence in the first paragraph). Moriya et al. further states that "[t]hese findings indicate that *once ectoderm has been induced to differentiate* by activin, there is a window of 3-5h in which retinoic acid can induce a very high rate of differentiation of pancreas-like structures" (emphasis added)(page 599, left column, beginning on line 5). Moriya et al. further states that "when isolated dorsal lips were treated with retinoic acid for 1-3h immediately after isolation they differentiated into pancreas (Moriya *et al.* 2000), *but dorsal lips had already begun to differentiate into endomesoderm*" (emphasis added) (page 598, left column, bottom of the paragraph).

Applicants note that the embryonic ectoderm disclosed in Moriya et al. is different from the claimed embryonic stem cells. Specifically, the embryonic ectoderm cells of Moriya et al. are destined to be "epidermis and neural tissue in normal development" (abstract); thus, they are not stem cells. The stem cells of the present invention are pluripotent cells, which are cells not yet destined to create any particular tissues or organs (excluding the placenta). Applicants note that the specification specifically states that the stems cells used in the present invention are undifferentiated cells.

Applicants further submit that claims 7 and 8 are not obvious under Moriya et al. in view of Takahashi et al. because, alone or in combination, Moriya et al. and Takahashi et al. do not teach all the elements of the claimed invention. Applicants note that Moriya et al., as described above, do not teach all the elements of the claimed invention. Takahashi et al. is merely cited for its disclosure of a retinoic acid X receptor ligand and fails to remedy the deficiencies of Moriya et al. Thus, Applicants submit that even if Moriya et al. were combined with Takahashi et al., the present invention would not result.

Applicants further respectfully submit that there is no reason to modify or combine the teachings of Moriya et al. and Takahashi et al. to arrive at the presently claimed invention. Applicants submit that the motivation alleged by the Office for combining the cited documents *would not have prompted a person of ordinary skill in the relevant field to arrive at the present invention*. The Action states that the motivation to combine Moriya et al. and Takahashi et al. was "to devise new therapeutic strategies against the incurable disease diabetes" (Office Action, page 6). Applicants respectfully submit that even if this were true, and that such motivation existed, one skilled in the art would not have combined these teachings, and the present invention certainly would not have resulted.

In view of the foregoing, Applicants respectfully request withdrawal of the outstanding rejections under 35 U.S.C. § 102(b) and 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, the Office is respectfully requested to withdraw the rejections of record and allow all the pending claims.

Applicants invite the Examiner to contact the undersigned with any questions.

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